The Two Faces of Telomerase

Richard Allsopp PhD
Assistant Professor
Institute for Biogenesis Research
University of Hawaii

Telomeres are genetic elements that cap and protect the ends of all chromosomes in eukaryotic cells, and are therefore, essential for chromosome stability. Telomerase, a ribonucleoprotein enzyme complex, is a specialized reverse transcriptase that functions to complete the replication of telomeres in dividing cells. Telomerase is composed of an essential RNA component (TR), which serves as a template during telomere replication, and an essential catalytic component called telomerase reverse transcriptase (TERT)(Figure 1). Most somatic cells in humans lack telomerase, and consequently telomeres shorten to some degree during aging in nearly all tissues comprised of mitotically active cells. On the other hand, telomerase is activated during pathogenesis of most cancers, allowing completion of telomere replication in these cells. Thus enhanced expression of telomerase in somatic cells has been proposed as an anti-aging therapy, whereas inhibition of telomerase in cancer cells has been proposed as a therapy for cancer treatment. Here I review the pros and cons of telomerase with regard to these potential therapeutic applications.

The physiological role of telomerase

The main function of telomerase is to complete telomere replication in the germ line (see figure). This has been proven in mice strains

Figure 1. The 'good' and 'bad' features of telomerase.

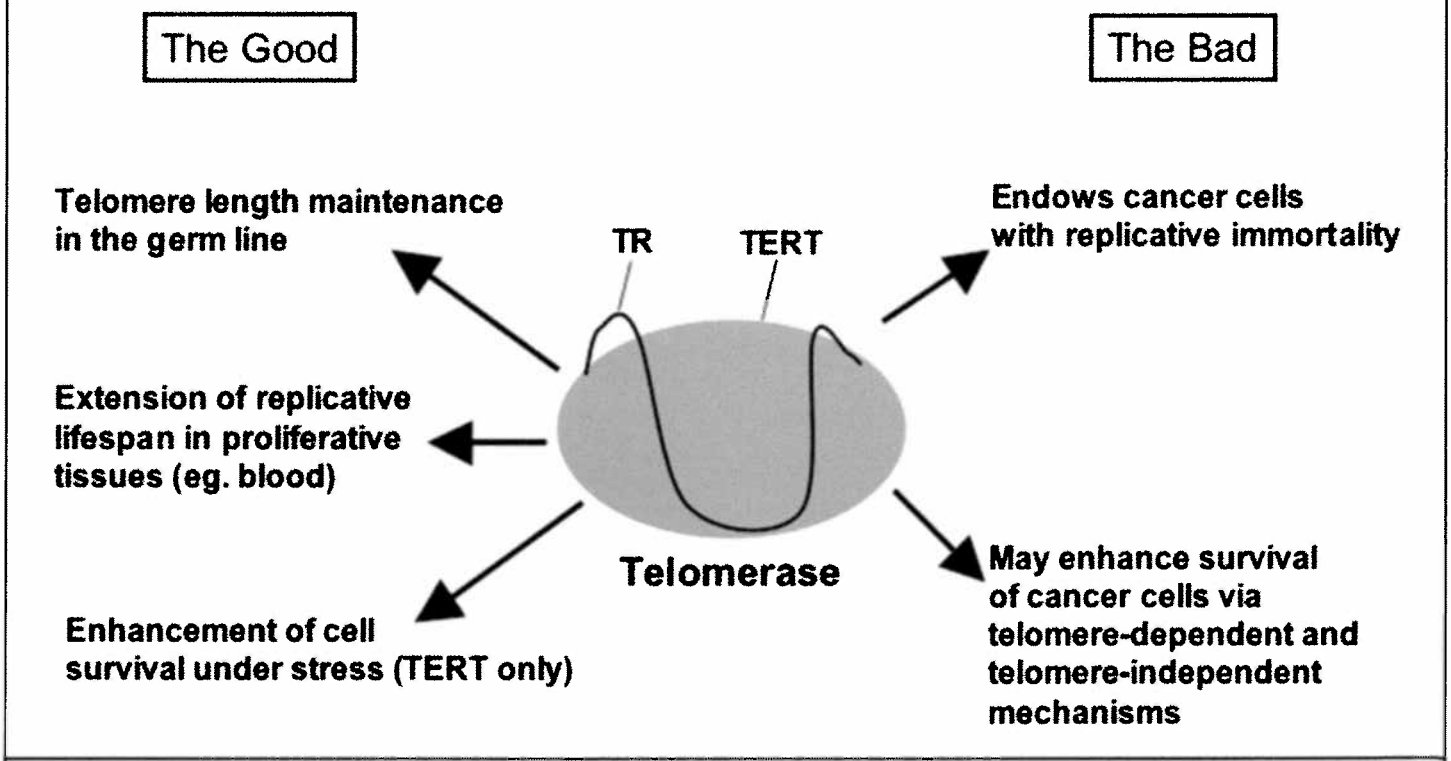

Figure 1.— The 'good' and 'bad' features of telomerase.

in which either the *TR* gene or *TERT* gene has been knocked out. Propagation of either the TR-/- [1] or TERT-/- [2] mice strain leads to continuous telomere erosion with each successive generation until, after three to five generations, depending on the strain, the loss of a telomere from one or more chromosomal ends becomes prevalent. The consequence is telomere dysfunction and cell cycle arrest at the cellular level, and an accelerated aging phenotype including sterility at the organismal level.

Telomerase also functions to slow the rate of telomere shortening in tissues with a relatively high turnover rate. This is primarily supported by analysis of telomere shortening during replicative aging of hematopoietic stem cells (HSC) from wild-type and telomerase deficient mice. Telomeres do shorten during replicative aging of the hematopoietic system, including HSC, in wild-type mice (and humans), despite the presence of telomerase activity at readily detectable levels in these cells. However, hematopoietic cells, including HSC, from early generation TR-/- or TERT-/- mice have been shown to have a roughly two-fold increase in the rate of telomere shortening and a markedly reduced replicative capacity relative to wild-type mice[3,4].

Finally, evidence is now emerging that suggests TERT may have a telomere-independent function in promoting cell survival in response to stress. For example, a transgenic model system has been developed to allow over-expression of TERT in basal keratinocytes[5]. These TERT transgenic mice exhibit enhanced wound healing capacity relative to wild-type mice. This is unlikely to be a result of telomere length maintenance in proliferating cells at the site of the wound since inbred mice have unusually long telomeres.

Telomerase and cancer

In humans, interestingly, telomerase was first detected in cancer cells (HeLa cells), not normal somatic cells[6]. Indeed, with the advent of the highly sensitive PCR-based TRAP assay for detection of telomerase activity, high throughput analysis of thousands of different tumor samples has demonstrated that >90% of human cancers express telomerase[7]. As in germ line cells, the activation of telomerase in cancer cells allows these cells to acquire replicative immortality. This was first shown during transformation of human embryonic kidney cells with SV40 large T antigen, where the rare emergence of immortal transformed colonies was shown to coincide with the activation of telomerase and telomere length maintenance[8]. We now know that one of the primary mechanisms for telomerase activation in cancer cells is the transcriptional activation of the *TERT* gene. In humans, most cells express moderate to low levels of TR, but no detectable levels of TERT. Furthermore, telomerase can be fully activated and telomeres elongated in various normal human somatic cells in vitro simply by the ectopic expression of TERT[9]. Two important conclusions may be drawn from this data. First, telomerase may be a very attractive candidate for cancer therapy. Preliminary studies have shown that inactivation of telomerase in vitro and in animal models leads to replicative arrest and/or death of tumor cells and loss of tumorigenicity in vivo[10]. Second, new targets for cancer therapy may emerge from a better understanding of the regulation of TERT expression.

More recently, data has emerged to suggest that telomere-independent functions of TERT may promote cancer development as well. This is evidenced by studies utilizing transgenic mice in which TERT over-expression in keratinocytes or blood cells leads to the predisposition or development of skin cancer[5] or lymphomas (Allsopp and Weissman, unpublished observations) respectively.

Telomerase: Fountain of youth or catalyst of death?

Clearly, telomerase plays an important role in the survival of most types of cancer, and thus extreme caution is warranted in the use of telomerase, or more specifically, TERT, as a therapy to rejuvenate old cells. On the other hand, there is no direct evidence to date to suggest that telomerase activation per se (ie. ectopic expression of TERT) predisposes human cells to a cancer phenotype. Transgenic studies in mice very often cannot be directly extrapolated to humans due to fundamental differences in biology. In particular, it is well established that mice cells are more easily transformed than human cells. Furthermore, there are significant differences in telomere and telomerase biology between mice and humans. The transient expression of TERT, under the control of a tightly regulated inducible promoter, in certain human cell types may very well turn out to be a safe and efficient way to re-set the replicative clock.

Also, as mentioned above, telomerase and proteins that regulate telomerase are likely to be useful targets for cancer therapy. However, the role of telomerase in the germ line and proliferative tissues should not be ignored in any telomerase-based cancer therapies, despite the normal phenotype of early generation telomerase knockout mice. Mice telomeres are, on average, four times longer than human telomeres, so the development of critically short telomeres upon inhibition of telomerase will be much quicker in humans than mice. Accurate targeting of any telomerase-based drugs to treat cancer will be important. In the end, it appears that we may be able to have our cake and eat it too with telomerase, as long as we are careful.

For more information on the Cancer Research Center of Hawaii, please visit our website at www.crch.org.

References

1. Blasco, M. et al. 1997. *Cell.* **91**. 25-34.
2. Liu, Y. et al. 2000. *Curr Biol.* **10,** 1459-1462.
3. Samper, E. et al. 2002. *Blood.* **99**, 2767-2775.
4. Allsopp R. et al. 2003. *Blood.* **102**, 517-520.
5. Gonzalez-Suarez, E. et al. 2001. *EMBO J.* **20**, 2619-2630.
6. Morin, G. 1989. *Cell.* **59**, 521-529.
7. Kim, N. et al. 1994. *Science.* **266**, 2011-2015.
8. Counter, C. et al. 1992. *EMBO J.* **11**, 1921-1929.
9. Bodnar, A. et al. 1998. *Science.* **279**, 349-352.
10. Hahn, W. et al. 1999. *Nat. Med.* **5**, 1164-1170.